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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,305	08/20/2001	Markus Albers	LEA33324	9002

7590 01/14/2004

EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/14/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/868,305	ALBERS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *03 December 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *26-34*.

Claim(s) objected to: _____.

Claim(s) rejected: *24,25 and 35-43*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *See Continuation Sheet*

Continuation of 3. Applicants definition that heteroatom means all non-carbon atoms coupled with their correct assertion that breadth is not indefiniteness is persuasive. According to the online free encyclopedia Wikipedia, "a heteroatom is any atom that is not carbon or hydrogen, typically, but not exclusively, nitrogen, oxygen, sulfur, phosphorus or boron." Thus, the indefiniteness rejection made in point # of the Final Rejection is withdrawn.

According to the German language version of the online free encyclopedia Wikipedia, the word "alkine" refers to hydrocarbons containing a carbon triple bond. The American heritage Dictionary offers "alkine" as a spelling variant of "alkyne". Thus, the indefiniteness rejection made in point #4 is withdrawn.

A terminal disclaimer was received on 5/27/03 for copending Application No. 09/828,514. Thus, the provisional double patenting rejection made in point #7 is overcome.

Continuation of 5. does NOT place the application in condition for allowance because: claims 35 and 36 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the other listed diseases of claim 35, does not reasonabl provide enablement for inhibiting angiogenesis generally.

Applicants argued that no analysis of all eight factors considered in making an enablement rejection had been completed. Firstly, ther is no requirement that all factors be cited in every enablement rejection. Secondly, the MPEP states in §2164.02 that Applicants lack of any working examples is an factor in the present speculative and unusual clinical arts.

Claims 24, 25, and 35-43 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,420,396 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound of claim 1 of U.S. Patent No. 6,420,396 B1 is a species embraced by the generic formula of the present claim 24. The compound of claim 1 of U.S. Patent No. 6,420,396 B1 fits formula (1) with R1 = R1, R2 = NR2'SO2R2", R2' hydrogen, R2" = C6H2(CH3)3, U = W = a direct bond, V= the alkylene group CH2, A = 1,4-phenylene, B = 1,3-phenylene, R3 = group (a14), and R4 = hydrogen. According to the MPEP §806.04(i) "Generic Claims Presented for First Time After Issue of Species. The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance o a copending application claiming plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See In re Braithwaite, 379 F.2d 594, 154 USPQ 29."

No disclaimer for U.S. Patent No. 6,420,396 B1 can be found in the file.

Continuation of 10. Other: Two FAXed documents have been received. A seven page FAX was received on 11/4/03 and a fifteen page FAX on 12/3/03. The latter FAX includes copies of the arguments made in the earlier FAX. This action is in response to arguments filed on 11/4/03. Applicant has made no amendments. There are twenty claims pending and twenty claims under consideration. Claims 24-2 are compound claims. Claim 43 is a composition claim. Claims 35-42 are use claims. Claims 28-34 are synthesis claims. This is the third action on the merits. The application concerns some biphenyl compounds, compositions, and uses thereof..

Mark L. Berch

PRIMARY EXAMINER
GROUP 120 - ART UNIT 1

DETAILED ACTION

Two FAXed documents have been received. A seven page FAX was received on 11/4/03 and a fifteen page FAX on 12/3/03. The latter FAX includes copies of the arguments made in the earlier FAX. This action is in response to arguments filed on 11/4/03. Applicant has made no amendments. There are twenty claims pending and twenty claims under consideration. Claims 24-27 are compound claims. Claim 43 is a composition claim. Claims 35-42 are use claims. Claims 28-34 are synthesis claims. This is the third action on the merits. The application concerns some biphenyl compounds, compositions, and uses thereof.

Response to Arguments

Applicants definition that heteroatom means all non-carbon atoms coupled with their correct assertion that breadth is not indefiniteness is persuasive. According to the online free encyclopediaWikipedia, "a heteroatom is any atom that is not carbon or hydrogen, typically, but not exclusively, nitrogen, oxygen, sulfur, phosphorus or boron." Thus, the indefiniteness rejection made in point #3 of the Final Rejection is withdrawn.

According to the German language version of the online free encyclopedia Wikipedia, the word "alkine" refers to hydrocarbons containing a carbon triple bond. The American heritage Dictionary offers "alkine" as a spelling variant of "alkyne". Thus, the indefiniteness rejection made in point #4 is withdrawn.

A terminal disclaimer was received on 5/27/03 for copending Application No. 09/828,514. Thus, the provisional double patenting rejection made in point #7 is overcome.

Claim Rejections - 35 USC § 112

Claims 35 and 36 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the other listed diseases of claim 35, does not reasonably provide enablement for inhibiting angiogenesis generally. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would inhibit angiogenesis in humans would require synthesis of the compound, formulation into

a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different human diseases described below and in healthy patients. Such a determination could also be performed by testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning inhibiting angiogenesis diseases is found in lines 9-16 page 87, which merely states Applicants' intention to do so. Applicants describe formulations in lines 18-27, page 87. Applicants do not teach which doses are required to practice their invention. Since no $\alpha_v\beta_3$ inhibitor has ever been used to treat any human disease, or to inhibit angiogenesis, how is the skilled physician to know what dose to use for each of these different diseases? There are two *in vitro* assays, drawn to αvβ3 receptor binding and cell migration described in pages 322-324 with data for eight compounds. It is neither stated in the specification nor recognized in the clinical arts that these two assays are correlated to clinical inhibition of angiogenesis generally. c) There is no working example of treatment of any disease in man or animals. There is no working example of any formulated drug required to practice these clinical claims. There is an *in vivo* assay concerning rat arteries described on page 323, but this assay appears to be prophetic and discloses no data. d) The nature of the invention is clinical treatment of disease as well as angiogenesis inhibition in normal humans,

which involves physiological activity. e) The state of the clinical arts in $\alpha_v\beta_3$ diseases is that no such inhibitor has ever shown the ability to inhibit angiogenesis generally. The state of the clinical art is that no physician would recognize why such a procedure should be applied to healthy volunteers.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 26 as well as the hundred of diseases embraced by the term inhibiting angiogenesis. According to the On-line Medical Dictionary at http://cancerweb.ncl.ac.uk/omd/index.html, angiogenesis is "The process of vascularisation of a tissue involving the development of new capillary blood vessels". As such it is a normal process occurring in healthy tissue, particular during development. This claim would read on inhibiting angiogenesis in mammals with below normal angiogenesis activity, inhibiting angiogenesis in mammals with normal angiogenesis activity, or in asymptomatic mammals with up-regulated angiogenesis activity. The specification fails to teach any benefit to

be gained from such actions. In fact, those actions would sound dangerous. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants argued that no analysis of all eight factors considered in making an enablement rejection had been completed. Firstly, there is no requirement that all factors be cited in every enablement rejection. Secondly, the MPEP states in §2164.02 that Applicants lack of any working examples is an factor in the present speculative and unusual clinical arts. Thirdly, all eight Wands factors are presented above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24, 25, and 35-43 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,420,396 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound of claim 1 of U.S. Patent No. 6,420,396 B1 is a species embraced by the generic formula of the present claim 24. The compound of claim 1 of U.S. Patent No. 6,420,396 B1 fits formula (1) with $R^1 = R^1$, $R^2 = NR^{2'}SO_2R^{2''}$, $R^{2'}$ = hydrogen, $R^{2''} = C_6H_2(CH_3)_3$, U = W = a direct bond, V= the alkylene group CH_2, A = 1,4-phenylene, B = 1,3-phenylene, R^3 = group (a14), and R^4 = hydrogen. According to

the MPEP §806.04(i) "Generic Claims Presented for First Time After Issue of Species. The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance of a copending application claiming plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29."

No disclaimer for U.S. Patent No. 6,420,396 B1 can be found in the file.